REMARKS

The Examiner has raised the following objections and rejections, summarized below in the order in which they are addressed:

I. Claims 35, 47, 62-63, 65-68, 71, 73, and 78-84 stand rejected under 35 U.S.C. §112, second paragraph as allegedly failing to particularly point out an distinctly claim the subject matter which the Applicants regard as their invention;

II. Claims 35, 47, 62, 63, 65-68, 71-73, and 78-84 stand rejected on the grounds of nonstatutory obviousness-type double patenting over U.S. Patent No. 7,195,871.

I. 35 U.S.C. §112, second paragraph

Claims 35, 47, 62-63, 65-68, 71, 73, and 78-84 stand rejected under 35 U.S.C. §112, second paragraph as allegedly failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention.

Claim 35 stands rejected as vague and indefinite because the Examiner asserts that it is unclear why step a) has a second cleavage structure without describing a first cleavage structure. While Applicants respectfully disagree, and submit that it is clear that a first cleavage structure is described as being formed in step (a)(iii) when "when the probe oligonucleotide is hybridized to the second portion of the target polynucleotide and the invader oligonucleotide is hybridized to the first portion of the polynucleotide", for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, step (a)(iii) is herein amended to recited the formation of a first cleavage structure. Applicants submit that the claim as amended meets the requirements of 35 U.S.C. §112, second paragraph and respectfully request that this rejection be withdrawn.

Claim 62 stands rejected as vague and indefinite because, while claim 77 requires that the non-target cleavage product is generated from the first nucleic acid molecule, the Examiner asserts that it is unclear how to generate said non-target cleavage product from said cleavage structure using a cleavage agent comprising a 5' nuclease, since Claim 62 does not require that the first nucleic acid contain an unpaired region in the first cleavage structure. Applicants respectfully submit that the specification provides ample instruction on the formation of a variety

of cleavage structures such that the claim is not unclear in view of the specification. Nonetheless, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, in the embodiment as presently claimed, Claim 62 is herein amended to recite that, when the first nucleic acid molecule is annealed to the target nucleic acid, the first nucleic acid molecule comprises a 5' portion that is not annealed to the target nucleic acid. Applicants submit that the claim as amended meets the requirements of 35 U.S.C. §112, second paragraph and respectfully request that this rejection be withdrawn.

Claim 62 stands rejected as vague and indefinite in that the Examiner asserts that it is unclear how the first cleavage structure can be formed in the presence of a cleavage agent comprising a 5' nuclease. Applicants respectfully point out that the specification provides numerous examples of cleavage structures forming in the presence of a 5' nuclease. Although an invasive cleavage reaction may for convenience be "started" by the addition of enzyme, and even if some structures form before the addition of the enzyme, numerous cleavage structures form and are cleaved on each copy of the target nucleic acid during the course of the reaction. See, *e.g.*, page 178, lines 26-27. The Description of the Invention also provides ample discussion of the formation and disassociation of cleavage structures during reactions, *i.e.*, in the presence of a cleavage agent comprising a 5' nuclease. See, *e.g.*, page 78, line 7 to page 81, line 2, and particularly the discussion at page 81, line5 to line 17, discussing how probes turn over and how a target nucleic acid is re-used to form additional structures with new (uncleaved) probes when a reaction is run at a temperature close to the T_m of the probe oligonucleotide. As such, it is abundantly clear that cleavage structures can and do form in the presence of a cleavage agent comprising a 5' nuclease. Applicants submit that the claim meets the requirements of 35 U.S.C. §112, second paragraph and respectfully request that this rejection be withdrawn.

Claim 69 stands rejected as vague and indefinite because the Examiner asserts that it is unclear how a thermostable 5' nuclease can comprise a 5' nuclease of a DNA polymerase. The Examiner asserts that nuclease and DNA polymerases are different enzymes. Applicants respectfully point the Examiner to the extensive discussion in the specification of polymerases that have, as part of their natural function, a 5' nuclease activity. See. *e.g.*, page 51, line 5 to page

52, line 22. Example 16, starting at page 182, demonstrates the use of 5' nucleases of DNA polymerases in cleaving cleavage structures, including enzymes having disabled or absent polymerase domains (*e.g.*, Cleavase® A/G and Cleavase® BN enzymes) and enzymes in which the nucleases are part of a functional polymerase protein (*e.g.*, *Thermus aquaticus*, *Thermus thermophilus*, and *Thermus flavus* DNA polymerases). As such, Applicants submit that a thermostable 5' nuclease can comprise a 5' nuclease of a DNA polymerase. Applicants therefore submit that the claim meets the requirements of 35 U.S.C. §112, second paragraph and respectfully request that this rejection be withdrawn.

Claim 77 stands rejected as vague and indefinite because the Examiner asserts that the phrase "said non-target cleavage product is generated in concentration excess compared to said duplex" does not make sense. Applicants respectfully disagree. With respect to "said duplex", the claim refers to the duplex between the target nucleic acid and the second nucleic acid molecule, as recited in Claim 75. As this duplex includes the target nucleic acid, it's concentration is limited to being less than or equal to the concentration of the target nucleic acid. As described above, however, probes (the nucleic acid in the cleavage structure that gets cut during the reaction, *i.e.*, first nucleic acid molecules) turn over, and the target nucleic acid is re-used to anneal new probes and form new cleavage structures. Thus, numerous probes (first nucleic acid molecules) are cleaved for each copy of the target nucleic acid during the course of the reaction. See, *e.g.*, page 178, lines 26-27. In this way, more copies of the probe are cleaved, and more copies of non-target cleavage product are produced, than there are copies of the target nucleic acid in the reaction. As such, the non-target cleavage product is generated in amounts in concentration excess compared to [the concentration of] the target, and therefore, necessarily, in concentration excess compared to [the concentration of] the second nucleic acid duplex. Applicants submit that the claim meets the requirements of 35 U.S.C. §112, second paragraph and respectfully request that this rejection be withdrawn.

Obviousness-Type Double Patenting

Claims 35, 47, 62, 63, 65-68, 71-73, and 78-84 stand rejected on the grounds of nonstatutory obviousness-type double patenting over U.S. Patent No. 7,195,871;

As each of this patent and the instant application are co-owned by the present Assignee, Applicants herein file a terminal disclaimer to obviate these rejections, and respectfully request that these rejections be removed.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that the reasons for all rejections have been addressed, and these rejections should be removed and Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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